

# The 2015 World Health Organization Classification of Tumors of the Pleura: Advances since the 2004 Classification



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## ABSTRACT

A new World Health Organization (WHO) Classification of Tumors of the Pleura has recently been published. While the histologic classification of pleural malignant mesothelioma remains the same in the 2015 WHO classification as it was in the 2004 classification, multiple new observations have been recorded. First, more detailed study has been performed of histologic subtyping of epithelioid mesothelioma. In particular, it has been recognized that the pleomorphic subtype is associated with a poor prognosis, similar to that of sarcomatoid malignant mesothelioma. Second, there is improved understanding of the role of immunohistochemistry in distinguishing mesothelioma from carcinomas of various sites. Third, the criteria for distinguishing malignant mesothelioma from reactive mesothelial proliferations has been further refined. Fourth, additional studies of sarcomatoid mesothelioma have defined the frequency and spectrum of various histologic and immunohistochemical features, including heterogeneous elements. Finally, pleural well-differentiated papillary mesotheliomas are better defined and cases with invasive foci are recognized. In addition, several promising observations in mesothelioma pathology and genetics have been made in the past decade. These are now the subject of further investigation to determine if they can be validated in ways that will significantly impact clinical practice. These include a preliminary study of grading, suggesting that nuclear atypia and mitotic count are independent prognostic markers. The discovery of inactivating mutations in the *BRCA1*-associated protein 1 gene in sporadic and hereditary mesothelioma has opened up a variety of novel molecular, clinical, and diagnostic investigations. One possible diagnostic application includes the setting of separating mesothelioma from

reactive mesothelial proliferations, where it may play a role in conjunction with *p16* FISH. Another useful discovery was that the *NAB2-STAT6* fusion is characteristic of solitary fibrous tumors. This led to development of a *STAT6* antibody that is a reliable immunohistochemical marker for solitary fibrous tumors. Genetic studies also led to the finding that *WWTR1-CAMTA1* fusions are useful diagnostic markers for epithelioid hemangioendotheliomas, which can present as pleural-based masses. Finally, desmoid type fibromatosis, a locally aggressive tumor that can present in the pleura, has been shown to frequently have *CTNNB1* gene mutations and express  $\beta$ -catenin by immunohistochemistry.

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**Keywords:** BAP1;  $\beta$ -catenin; Biphasic; *CTNNB1* gene mutations; Desmoid; Desmoplastic; Epithelioid; Epithelioid hemangioendothelioma; Grading; Mesothelioma; *p16*; Sarcomatoid; Solitary fibrous tumor; *STAT6*; *WWTR1-CAMTA1*

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## Introduction

The 2015 World Health Organization (WHO) Classification of Tumors of the Pleura has recently been published.<sup>1,2</sup> While the histologic classification of malignant mesothelioma remains the same in the 2015 WHO classification (Table 1) as it was in the 2004 WHO classification,<sup>3</sup> multiple new observations have been reported. Diffuse malignant mesothelioma (DMM) needs to be distinguished from other mesotheliomas that have a much better prognosis, including localized malignant mesotheliomas (LMMs) and well-differentiated papillary mesotheliomas (WDPMs). The purpose of this article is to present the 2015 WHO classification of pleural tumors and to summarize some of the advances since 2004 that impact the improved diagnosis of pleural tumors.

## Pleural Malignant Mesothelioma: Significant Advances

### Histologic Subtyping of Epithelioid Mesothelioma

The major histologic types of DMM, including epithelioid, sarcomatoid, and biphasic, are well recognized, and patients with sarcomatoid and biphasic tumors have significantly poorer survival compared to patients with epithelioid DMMs.<sup>4,5</sup> Within the category of pleural epithelioid DMMs, while a variety of morphologic subtypes are recognized—including tubulopapillary, papillary, micropapillary, trabecular, solid, and pleomorphic—there have

been few comprehensive studies examining the prognostic importance of these patterns. Several recent studies have addressed this topic, revealing an aggressive behavior of epithelioid DMMs with pleomorphic features.<sup>6–8</sup>

Tumors with anaplastic or prominent giant cells, often multinucleated, are designated pleomorphic (Fig. 1A). Two studies demonstrated significantly poorer prognosis for the pleomorphic subtype of epithelioid DMM compared to other epithelioid tumors, and survival was similar to that of patients with biphasic and sarcomatoid DMMs.<sup>6,8</sup> While both papers proposed that the pleomorphic pattern be reclassified from the epithelioid to the sarcomatoid subtype, this was not accepted by the WHO panel. According to the 2015 WHO classification, these tumors are regarded as a poor prognostic subset of epithelioid DMMs. In addition, after excluding the pleomorphic tumors, Kadota et al.<sup>8</sup> showed that the combined group of tubulopapillary and trabecular tumors had a more favorable prognosis than the solid subtype and the combined solid/micropapillary group (Fig. 1B and C). Brcic et al.<sup>6</sup> also showed substantial interobserver reproducibility among two observers in the histologic subtyping of epithelioid DMMs. These findings are promising in that histologic subtyping of epithelioid DMMs may help to identify prognostic subsets and that these may be reproducible. However, more data are needed on this subject before histologic subtyping can be formally introduced into the classification of pleural epithelioid DMMs.

**Table 1.** World Health Organization Classification of Tumors of the Pleura

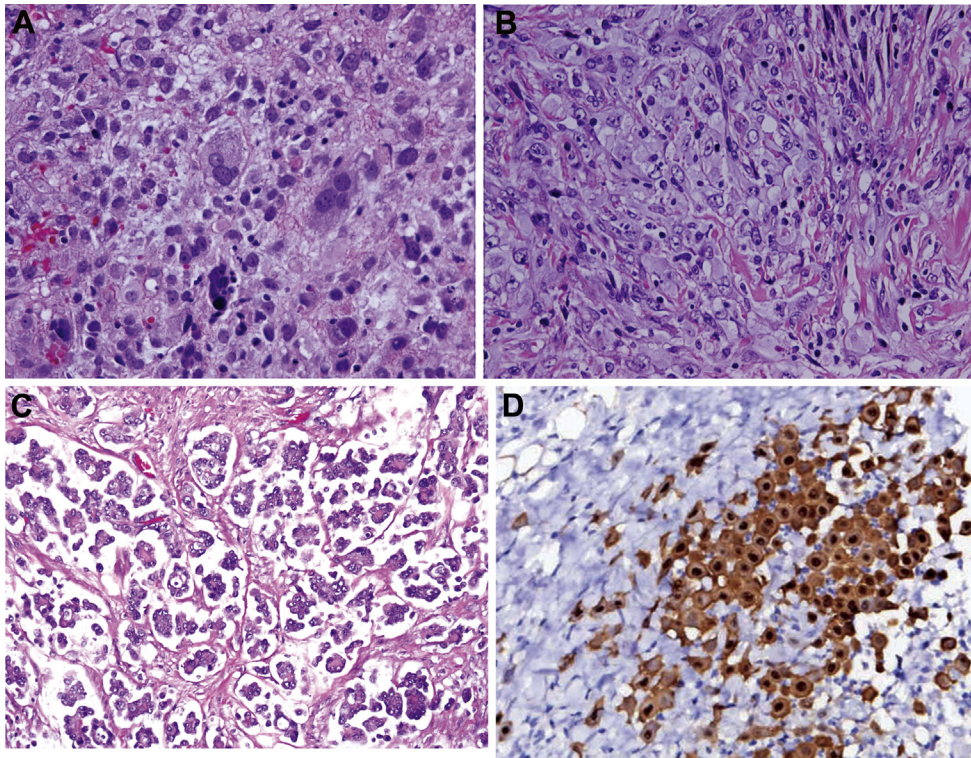
	ICD-O Code <sup>a</sup>		ICD-O Code <sup>a</sup>
<b>Mesothelial tumors</b>		<b>Mesenchymal tumors</b>	
Diffuse malignant mesothelioma		Epithelioid hemangioendothelioma	9133/3
Epithelioid mesothelioma	9052/3	Angiosarcoma	9120/3
Sarcomatoid mesothelioma	9051/3	Synovial sarcoma	9040/3
Desmoplastic mesothelioma	9051/3	Solitary fibrous tumor	8815/1
Biphasic mesothelioma	9053/3	Malignant solitary fibrous tumor	8815/3
Localized malignant mesothelioma		Desmoid-type fibromatosis	8821/1
Epithelioid mesothelioma	9052/3	Calcifying fibrous tumor	8817/0
Sarcomatoid mesothelioma	9051/3	Desmoplastic round cell tumor	8806/3
Biphasic mesothelioma	9053/3		
Well differentiated papillary mesothelioma	9052/1 <sup>b</sup>		
Adenomatoid tumor	9054/0		
<b>Lymphoproliferative disorders</b>			
Primary effusion lymphoma	9678/3		
Diffuse large B-cell lymphoma associated with chronic inflammation	9680/3		

Adapted with permission from Travis et al.<sup>1</sup>

<sup>a</sup>Morphology codes are taken from the ICD-O.<sup>58</sup> Behavior is coded /0 for benign tumors, /1 for unspecified, borderline, or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

<sup>b</sup>This new code was approved by the International Agency for Research on Cancer/World Health Organization Committee for the International Classification of Diseases for Oncology.

ICD-O, International Classification of Diseases for Oncology.



**Figure 1.** Diffuse malignant mesothelioma, epithelioid type. (A) The pleomorphic pattern consists of large atypical and multinucleated tumor cells, some with prominent nucleoli. (B) The solid pattern, with sheets of epithelioid tumor cells. (C) The micropapillary pattern, with a nest of tumor cells growing in papillae lacking fibrovascular cores. (Reprinted from Travis et al.<sup>1</sup>, with permission from Dr. William D. Travis.) (D) Staining with calretinin shows positive nuclear and cytoplasmic reactivity. (Reprinted from Travis et al.<sup>1</sup>, with permission from Dr. Françoise Galateau-Salle.)

### Immunohistochemistry in Malignant Mesothelioma Diagnosis

There is an improved understanding of the role of immunohistochemistry in distinguishing malignant mesothelioma from carcinomas of various sites.<sup>9</sup> In the 2004 WHO classification, the discussion of immunohistochemical markers to distinguish malignant mesothelioma from carcinomas was limited to the general carcinoma markers.<sup>3</sup> However, in a subsequent guideline from the International Mesothelioma Interest Group,<sup>9</sup> more detail was provided on the recommended workup for the separation of mesothelioma from various carcinomas, including lung, breast, ovarian, colonic, squamous cell, and renal cell carcinoma. Site-specific carcinoma marker panels are introduced in the 2015 WHO classification (Table 2). However, there are no site-specific antibodies that are 100% specific and sensitive for metastatic carcinomas from most organs; therefore, panels of antibodies are recommended.

The most common circumstance in which immunohistochemistry provides an aid to the diagnosis of malignant mesothelioma is the separation of the epithelioid variant of mesothelioma from other carcinomas that might involve the pleura.<sup>9</sup> The most common differential diagnostic consideration in this regard is with primary

adenocarcinoma of the lung. Specificity and sensitivity considerations support the use of calretinin (Fig. 1D), cytokeratins 5/6, WT-1, and D2-40 as positive mesothelial markers, and carcinoembryonic antigen (CEA), B72.3, Bg8, BerEP4, and MOC-31 as positive carcinoma markers (Table 2).<sup>9</sup> In this situation, the use of at least two of these mesothelial markers and two of these carcinoma markers in addition to TTF-1 is recommended.

A number of organ-specific markers are also of use to help exclude metastatic disease from certain primary sites. These include TTF-1 and Napsin A for adenocarcinoma of the lung, PAX-8 for renal cell and thyroid carcinoma, prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) for adenocarcinoma of the prostate, CDX2 and cytokeratin 20 for adenocarcinoma of the gastrointestinal tract, and PAX-8, PAX-2, and estrogen receptor (ER) for serous papillary carcinoma of the ovary or peritoneum.<sup>9</sup> Several markers for carcinoma of the breast also have use, including estrogen receptor, progesterone receptor, gross cystic disease fluid protein (GCDFFP)-15, and mammaglobin. It should be noted that a relatively new marker for breast and bladder cancers, GATA-3, is expressed in more than half of mesotheliomas and therefore has limited or no use in this regard.<sup>10</sup>



**Table 2.** Immunohistochemistry of Epithelioid Malignant Mesothelioma

Mesothelial Markers		
Markers	Sensitivity	Specificity versus Lung Adenocarcinoma
Calretinin	> 90%	90%-95%
CK5/6	75%-100%	80%-90%
WT1	70%-95%	~100%
D2-40	90%-100%	85%
Adenocarcinoma (Positive Epithelial Markers)		
Markers	Sensitivity	Specificity versus Malignant Mesothelioma
MOC31	95%-100%	85%-98%
BerEP4	95%-100%	74%-87%
BG8 (Lewis Y)	90%-100%	93%-97%
B72.3	25%-85%	> 95%
Monoclonal carcinoembryonic antigen	80%-100%	> 95%
Organ Specific - Lung		
Markers	Sensitivity	Specificity versus Malignant Mesothelioma
TTF1 (8G7G3/1)	~80%	High
Napsin A	~80%	High
Organ Specific - Breast		
Markers	Sensitivity	Specificity versus Malignant Mesothelioma
Estrogen receptor $\alpha$	NA	NA
Progesterone receptor	NA	NA
GCDFP15	30%-40%	High
Mammaglobin	50%-85%	High
Organ Specific - Renal		
Markers	Sensitivity	Specificity versus Malignant Mesothelioma
PAX8	70%-100%	Unknown
PAX2	80%	Unknown
RCC	$\leq$ 85%	75%-90%
CD15 (LeuM1)	60% <sup>a</sup>	High

Adapted with permission from Travis et al.<sup>1</sup><sup>a</sup>Variable by subtype.

CEAm, monoclonal carcinoembryonic antigen; NA, not available.

In an occasional case of epithelioid DMM, the morphology may somewhat resemble squamous cell carcinoma. In this situation, p40 (or p63) immunohistochemistry is useful, because nuclear staining with these

antibodies is strongly and diffusely positive in squamous cell carcinoma but not in mesothelioma. Staining for cytokeratins 5/6 is of no use in this differential diagnosis because both epithelioid mesothelioma and squamous cell carcinoma stain strongly positive for this marker.<sup>11</sup>

A broad spectrum immunohistochemical stain for cytokeratins also has some use, because lack of staining of an epithelioid neoplasm involving the pleura with this marker would raise a different set of differential diagnostic considerations, including large cell lymphoma, malignant melanoma, epithelioid hemangioendothelioma, and epithelioid angiosarcoma.<sup>9</sup> Useful hematopoietic markers include CD45 and CD20. Similarly, HMB45, melan A, and SOX10 are useful markers for melanoma. Endothelial markers such as CD31, CD34, v-ets avian erythroblastosis virus E26 (ERG), and Fli-1 have use in the diagnosis of rare cases of angiosarcoma or epithelioid hemangioendothelioma involving the pleura (see below).<sup>9</sup> As a precaution, it should be noted that these latter two endothelial-derived malignancies may show some staining for cytokeratins, although it is usually focal. In addition, immunostaining for broad spectrum cytokeratins may be helpful in the diagnosis of desmoplastic DMM, especially for the identification of invasion of adipose tissue or lung parenchyma by keratin-positive spindle cells.

Immunohistochemistry has a more limited role in the separation of sarcomatoid malignant mesothelioma from other sarcomas and sarcomatoid malignancies that involve the pleura (Table 2). The vast majority of sarcomatoid mesotheliomas stain positive for broad-spectrum anticytokeratin antibodies, whereas most soft tissue sarcomas do not.<sup>12</sup> Keratin stains can be negative in approximately 5% of sarcomatoid mesotheliomas and 10% of tumors with heterologous elements.<sup>12,13</sup> A useful role of keratin staining in the setting of sarcomatoid DMM is in revealing the invasion of tumor cells into fat. Calretinin is seen in only about 30% of cases, including those with heterologous elements.<sup>12,13</sup> Mesothelial markers useful for the diagnosis of epithelioid mesothelioma are rather insensitive for sarcomatoid mesotheliomas, the majority of which are negative for calretinin, cytokeratin 5/6, and WT-1. These tumors are more often positive for D2-40. Sarcomatoid mesotheliomas are typically positive for vimentin and may also show positivity for S-100, actin, or desmin, but these markers have no diagnostic specificity.

One must be particularly careful to distinguish sarcomatoid mesothelioma from other sarcomatoid malignancies involving the pleura that may be positive for cytokeratins. Monophasic synovial sarcomas may be identified by demonstrating the SYT-SSX fusion protein by fluorescence in situ hybridization (FISH). Sarcomatoid carcinomas may be positive for TTF-1, Napsin A, or

**Table 3.** Reactive Atypical Mesothelial Hyperplasia versus Epithelioid Malignant Mesothelioma

Histological Features	Atypical Mesothelial Hyperplasia	Malignant Mesothelioma
<b>Major criteria</b>		
Stromal invasion	Absent	Present (the deeper the more definitive)
Cellularity	Confined to the pleural surface	Dense, with stromal reaction
Papillae	Simple, lined by single-cell layer	Complex, with cellular stratification
Growth pattern	Surface growth	Expansile nodules, complex and disorganized pattern
Zonation	Process becomes less cellular towards chest wall	No zonation of process, often more cellular away from effusion
Vascularity	Capillaries are perpendicular to the surface	Irregular and haphazard
<b>Minor criteria</b>		
Cytological atypia	Confined to areas of organizing effusion	Present in any area, but many cells are deceptively bland and relatively monotonous
Necrosis	Rare (necrosis may be within pleural exudates)	Necrosis of tumor area is usually a sign of malignancy
Mitoses	Mitoses may be plentiful	Many mesotheliomas show few mitoses (but atypical mitoses favor malignancy)

Adapted with permission from Travis et al.<sup>1</sup>

p40 (or p63), depending on whether adenocarcinoma or squamous differentiation is present. Another differential diagnosis that occasionally arises is separation of sarcomatoid mesothelioma from solitary (localized) fibrous tumors of the pleura. The latter stain positive for CD34 and bcl-2, and are usually keratin-negative. As described below, more recently, these tumors have been shown to be positive for STAT6 (Table 2).<sup>14</sup> Separation of sarcomatoid DMM and solitary fibrous tumor (SFT) is usually not difficult because most of the latter are benign. However, it can be challenging with malignant SFTs where CD34 expression is lost. In this setting, the gross appearance can be helpful because DMMs typically cause diffuse pleural thickening, and SFTs are localized masses, even when malignant. In addition, most DMMs are positive for cytokeratin stains while SFTs are typically negative, and STAT6 is usually positive in SFTs and negative in DMMs.

### Separation of Benign from Malignant Mesothelial Proliferations

Since 2004, the criteria for distinguishing malignant DMM from reactive mesothelial proliferations have been refined.<sup>15–19</sup> Morphologic criteria for distinguishing epithelioid malignant DMMs from reactive mesothelial hyperplasia and organizing pleuritis (or chronic fibrous pleuritis) are recognized (Table 3).<sup>1,18,20</sup> However, in many cases, application of these criteria are challenging for a variety of reasons, including the size of the biopsy specimen, sampling problems, entrapment of mesothelial cells, and tangential cuts.<sup>1,18</sup>

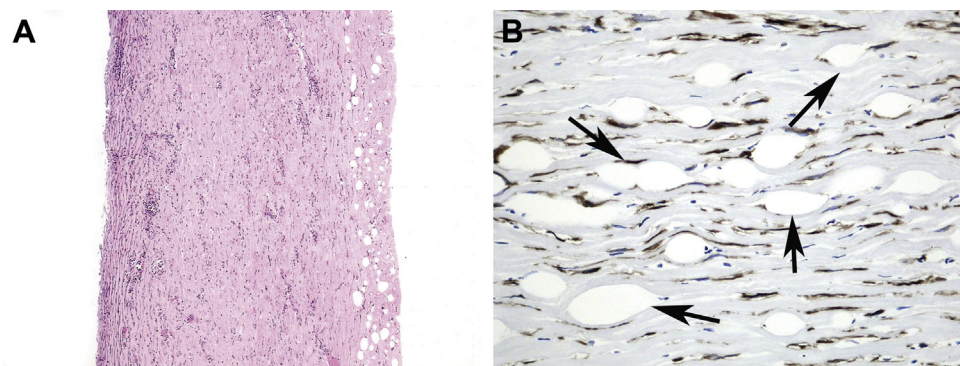
**Morphology.** The separation of benign from malignant mesothelial proliferations remains a difficult problem. The new classification reemphasizes the idea that unless one has overt tumor fragments, invasion of the

stroma remains the single best criterion for diagnosing malignant mesothelioma. Pan-keratin stains can be extremely helpful in showing subtle invasion that may not be readily apparent on hematoxylin-eosin-stained specimens.

Zonation—increased cellularity immediately under the pleural effusion (sometimes associated with marked cytologic atypia right under the effusion) and a progressive decrease in cellularity away from the effusion—is a useful marker of a benign process (Fig. 1A); mesotheliomas, on the other hand, may show greater cellularity away from the effusion or homogeneously high cellularity throughout a greatly thickened pleura. Layering of mesothelial cells interspersed with collagen immediately adjacent to the pleural space is also a sign of a benign reaction; the layering represents repeated effusions that organize, leaving a mesothelial layer and underlying fibrosis (Fig. 1A).

Because invasion is by far the best marker of mesothelial malignancy, mesothelial proliferations confined to the pleural surface represent an ongoing problem without a good solution. Heaped up masses of mesothelial cells are suggestive of malignancy, but this is not always true; conversely, simple papillae with a single layer of covering cells are more typical of a benign reaction—but again, this is not always true. Judging from cases that have both a surface proliferation and underlying invasive mesothelioma, many surface proliferations are simply extensions of an invasive tumor onto the pleural surface, and *p16* FISH is potentially useful in marking such cases (see below).<sup>17</sup> True mesothelioma in situ presumably exists, but at this point there are no criteria to allow that diagnosis, and the use of this term is discouraged.

Desmoplastic mesothelioma versus organizing pleuritis presents a somewhat different set of morphologic



**Figure 2.** Organizing pleuritis. (A) The pleural cavity is on the left, and the chest wall fat (not sampled) would appear on the right. The biopsy specimen reveals zonation—that is, it is more cellular adjacent to the pleural cavity and less cellular away from the pleural cavity. In addition, there is layering of mesothelial cells immediately adjacent to the pleural space; this is a sign of a benign process. This particular example shows fake fat located deep in the pleura near the junction with the chest wall; note the characteristic pattern of fat-like spaces parallel to the pleura surface (right). (B) Keratin staining of an area of fake fat from another case. Keratin-positive mesothelial cells run between the spaces (highlighted by arrows), suggesting the invasion of fat. However, all of the mesothelial cells are aligned parallel to the pleural surface and do not invade down (i.e., away from the pleural surface), the diagnostic finding that would be seen in desmoplastic mesothelioma.

problems.<sup>18,20,21</sup> Desmoplastic mesotheliomas typically have a short storiform pattern (“patternless pattern”) of cells in haphazardly arranged slits between collagen bundles. Again, invasion of the stroma (usually chest wall fat) is by far the best criterion of malignancy, and pan-keratin stains should be used to highlight invasion. As is true of epithelial mesothelial processes, zonation is also helpful in making this separation, because desmoplastic mesotheliomas do not show zonation. The presence of expansile stromal nodules, areas of frankly sarcomatous tumor, and bland necrosis all favor desmoplastic mesothelioma, but these criteria are not as robust as invasion. The presence of a focal, clearly malignant, epithelioid component can also support a diagnosis of malignancy.

A phenomenon that represents a source of confusion is so-called “fake fat,” an artifact related to traction caused by obtaining biopsy specimens from densely fibrotic pleura<sup>19</sup> (Fig. 2A and B). Fake fat consists of rounded to elongated spaces aligned parallel to the pleural surface in thickened and fibrotic pleura; the spaces are most often near the junction of the fibrotic pleura with the chest wall fat. When the spaces are elongated, they are elongated parallel to the pleural surface. True fat stains for S-100 or calretinin, whereas the spaces of fake fat stain for neither, but often contain weakly hematoxyphilic flocculent material. All active benign or malignant mesothelial processes are pan-keratin–positive, and one of the things that makes fake fat treacherous is the presence of pan-keratin–positive, benign reactive mesothelial cells coursing between the spaces (Fig. 2B); at first glance, there appears to be invasion of fat. However, in desmoplastic mesotheliomas, invasive pan-keratin–positive cells always spread downward at an angle to the pleural surface into the underlying true fat or chest wall muscle, whereas with fake fat the keratin-positive cells are always located in the

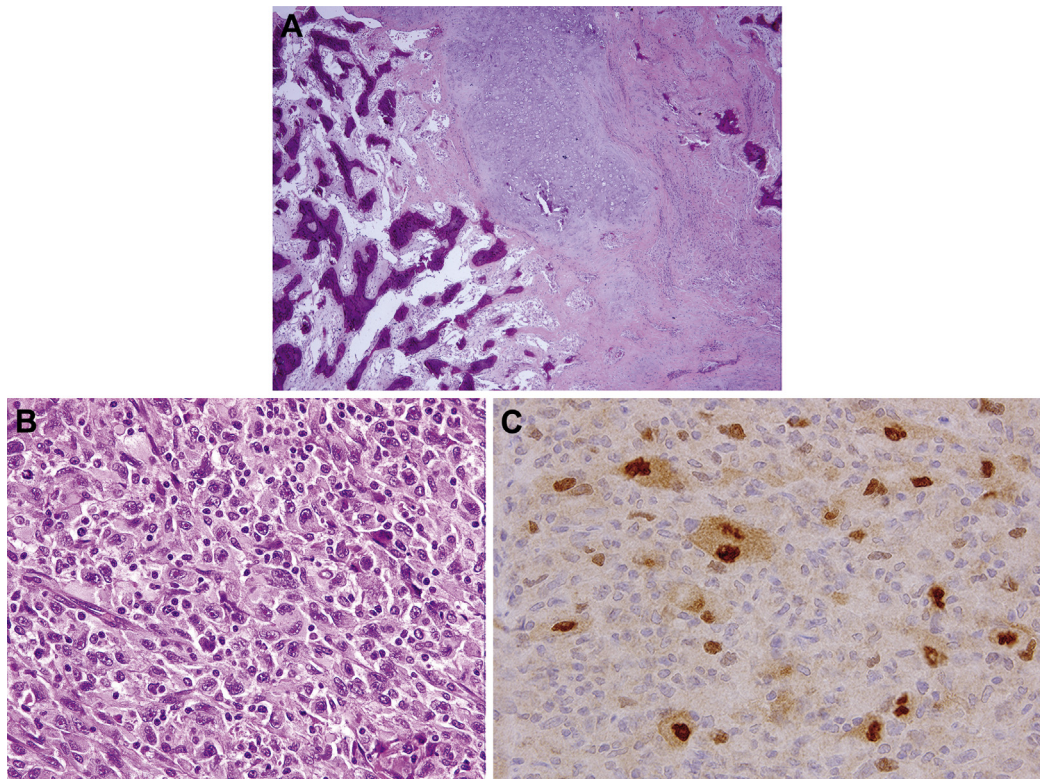
densely fibrotic pleura and run parallel to the pleural surface (Fig. 2B).

**Immunohistochemical Findings.** A variety of immunohistochemical stains have been proposed as markers of either benign mesothelial processes (desmin) or mesothelioma (e.g., p53, EMA, GLUT-1, and IMP-3). None of these markers has an established molecular or metabolic basis, all of them show overlap between benign and malignant, and at best they provide statistical differences in large series but are of little value in individual cases.<sup>18</sup> Even GLUT-1, which is linked to cellular metabolic activity (essentially the same process that drives positron emission tomography scans), stains some benign reactions. Another problem is that red blood cells stain intensely for GLUT-1, making interpretation difficult. Recent analysis of data regarding immunohistochemistry for EMA, GLUT-1, and IMP-3 suggests these markers are not useful in this setting.<sup>16</sup> The molecular markers of *p16* FISH and *BRCA1*-associated protein 1 (*BAP1*) immunohistochemistry have shown promise in helping to distinguish benign from malignant mesothelial proliferations, as explained below.

### ***Sarcomatoid Mesothelioma with and without Heterologous Elements***

Since 2004, several comprehensive studies of sarcomatoid DMM have better defined the frequency and spectrum of various histologic and immunohistochemical features, including heterologous elements.<sup>12,13</sup> In one study of 326 cases, histologic review showed that 44% were conventional sarcomatoid tumors, desmoplastic foci were seen in 34% of cases, but 21% of sarcomatoid mesotheliomas were classified as desmoplastic mesothelioma, 2% had osteosarcomatous and or





**Figure 3.** Diffuse malignant mesothelioma, sarcomatoid type with heterologous elements. (A) Malignant bone and cartilage represent osteosarcomatous and chondrosarcomatous differentiation in this malignant mesothelioma. (B) Rhabdomyosarcomatous differentiation in this mesothelioma shows highly atypical tumor cell cytology with prominent epithelioid cytoplasm, suggesting rhabdomyoblasts. (C) Immunohistochemistry of the tumor in part B shows positive staining for myogenin, confirming rhabdomyosarcomatous differentiation. (B and C, Reprinted from Travis et al.<sup>1</sup>, with permission from Dr. William D. Travis.)

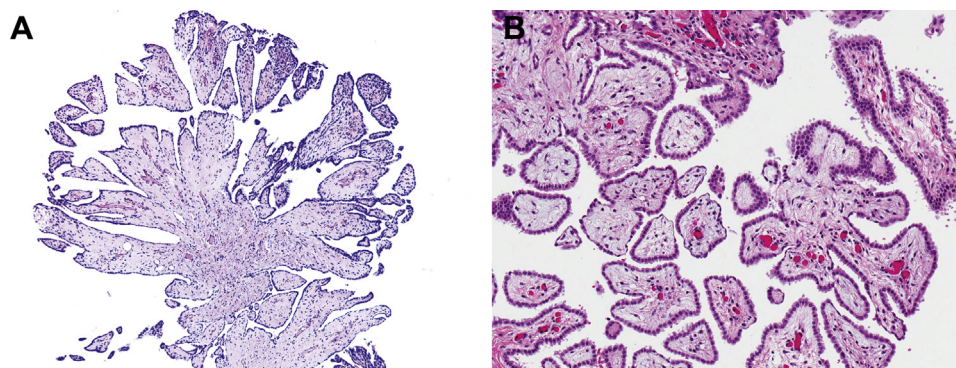
chondrosarcomatous differentiation, and <1% had a lymphohistiocytoid pattern.<sup>12</sup> When heterologous elements are present, they most often consist of osteosarcomatous elements followed by a mixture of chondrosarcoma and osteosarcoma (Fig. 3A), rhabdomyosarcoma, and chondrosarcoma only.<sup>13</sup> In some tumors with rhabdomyosarcomatous differentiation, the morphology may only be suggestive and the diagnosis requires confirmation with myogenin (Fig. 3B and C) or MyoD1,<sup>1,13</sup> or the specific PAX3/7-FOXO1 fusion by FISH.<sup>22</sup> These tumors need to be distinguished from primary and secondary pleural sarcomas, including osteosarcomas and chondrosarcomas, and carcinosarcomas of the lung. In the setting of a tumor showing diffuse pleural thickening with heterologous elements, even if the keratin stain is negative, by convention the diagnosis of malignant mesothelioma is preferred over osteosarcoma, chondrosarcoma, or rhabdomyosarcoma.<sup>1,13</sup>

As described above, sarcomatoid DMMs can rarely be keratin-negative, and most are negative for mesothelial markers, such as calretinin. The diagnosis of malignant mesothelioma can be made in the absence of keratin and calretinin expression if the morphologic, clinical, and radiologic features are otherwise consistent with

mesothelioma. In particular, there should be diffuse pleural thickening with absence of an intrapulmonary mass or a history of soft tissue sarcoma.

### Well-Differentiated Papillary Mesothelioma

Several articles have better defined the pathologic and clinical features of pleural WDPMs.<sup>23,24</sup> While WDPMs are more frequently found in the peritoneal cavity, these tumors have similar clinical and pathologic features. WDPM represents a distinct mesothelial tumor characterized histologically by superficial spreading of papillary formations with broad fibrovascular cores, often with myxoid stroma (Fig. 4A and B). They are lined by bland, flattened, or epithelioid mesothelial cells, without or with limited invasion of the submesothelial layer. Invasion can consist of invasion of stalks of papillae by bland-appearing cells or cytologically higher grade solid foci. The major challenge in diagnosis is separation from papillary forms of conventional DMM. This may be difficult in small biopsy specimens. Solid foci of tumors favor DMM. Correlation with radiologic and operative findings is important. WDPMs typically form small translucent nodules in contrast to DMMs, which typically have solid nodules or diffuse pleural



**Figure 4.** Well differentiated papillary mesothelioma. (A) This tumor consists of exophytic surface growth on the pleural surface, consisting of papillary fronds with broad fibrovascular cores. No downward invasive growth was seen. (Reprinted from Travis et al.<sup>1</sup>, with permission from Dr. Francoise Galateau-Salle.) (B) These papillae have broad fibrovascular cores with a myxoid stroma. The surface of the papillae is lined by cuboidal mesothelial cells with bland cytology.

thickening by a rind of tumor. The former have an indolent clinical outcome, and in most cases are clinically benign if completely resected.<sup>23</sup> Whether WDPMs can progress to DMMs is uncertain. WDPMs with invasive foci confined to the stalk are prone to recurrences but are rarely fatal.<sup>24</sup>

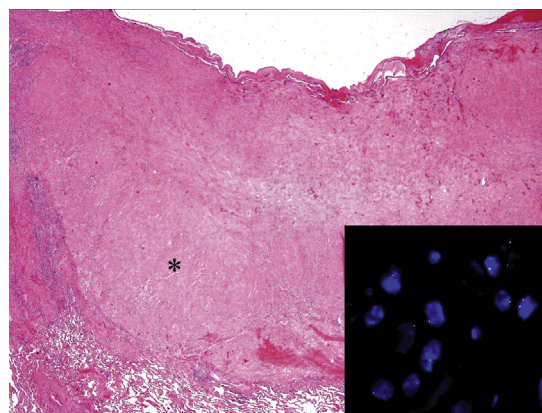
### Pleural Malignant Mesothelioma: Promising Advances

Over the past decade, several observations have been made in mesothelioma pathology and genetics that have promise to significantly impact clinical practice. These are now the subject of further investigation to determine if they can be validated. These include histologic grading, use of *BAP1* immunohistochemistry and *p16* FISH in separation of DMM from reactive mesothelial proliferations, use of *STAT6* immunohistochemistry for diagnosis of solitary fibrous tumor, and FISH for the *WWTR1/CAMTA1* fusion for diagnosis of epithelioid hemangioendothelioma and  $\beta$ -catenin immunohistochemistry<sup>25</sup> and *CTNNB1* mutation<sup>26</sup> for the identification of sporadic, desmoid-type fibromatosis located in the pleura.

### Histologic Grading of Diffuse Malignant Mesothelioma, Epithelioid Type

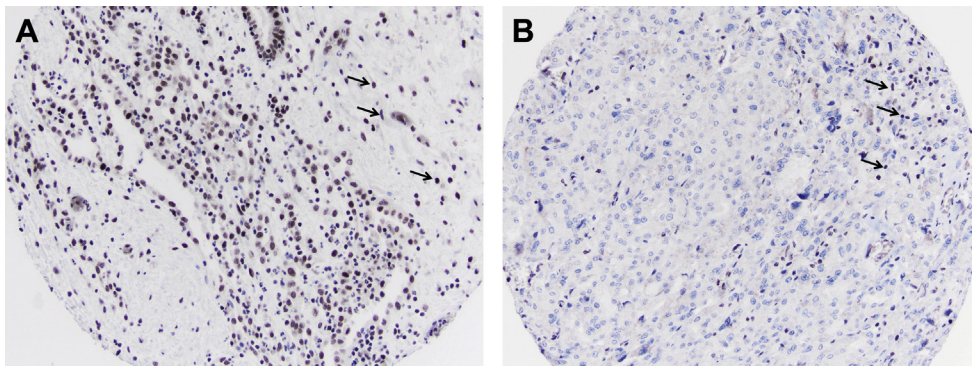
Histologic grading is inherently built into the histologic typing of DMM because most studies show that epithelioid tumors have the best prognosis with decreased survival for biphasic followed by sarcomatoid tumors.<sup>4,5</sup> Because the prognosis for biphasic and sarcomatoid DMMs is so poor, it is mainly in the lower grade epithelioid DMMs that there is an opportunity to show prognostic significance to grading. However, there is no established histologic grading system for epithelioid DMMs. A preliminary study proposed a grading system for pleural DMM using nuclear atypia and mitotic count.<sup>27</sup> In this study, nuclear atypia, chromatin pattern, prominence of nucleoli, mitotic count, and atypical mitoses

correlated with poor survival by univariate analysis. Multivariate analysis showed that nuclear atypia and mitotic count were independent prognostic factors. These two factors were used to create a three-tier nuclear grade score that stratified patients into three distinct prognostic groups: grade I ( $n = 107$ ; median overall survival, 28 months), grade II ( $n = 91$ ; median overall survival, 14 months), and grade III ( $n = 34$ ; median overall survival, 5 months).<sup>27</sup> When analyzed with other clinicopathologic factors, this nuclear grading system was a stronger discriminator of both overall survival and time to recurrence. Unfortunately, there are no other published studies to date that have attempted to validate this in pleural mesothelioma. A recent article evaluating peritoneal epithelioid mesotheliomas found that a high mitotic rate was associated with poor overall survival, although this was only shown by univariate analysis.<sup>28</sup>



**Figure 5.** Utility of *p16* fluorescence in situ hybridization (FISH) to separate benign from malignant mesothelial proliferations. This patient was thought to have a mesothelioma, but the biopsy specimen was equivocal with vague stromal nodules (marked with an asterisk), suggestive of a desmoplastic mesothelioma. FISH (inset) reveals a complete loss of red *p16* signals, indicating that the process is in fact malignant. Green signals represent centromere 9.





**Figure 6.** *BRCA1*-associated protein 1 (*BAP1*) immunostaining in mesothelioma. These examples of mesotheliomas show the (A) retention and (B) loss of *BAP1* from a tissue microarray. Arrows point out positive stromal cells and lymphocytes that serve as internal staining controls.

### Diagnostic Tests Based on Newly Recognized Molecular Abnormalities

The most common genetic changes in DMM are inactivation of the tumor suppressor gene *NF2*; deletion of the *9p21* locus, which harbors *p16INK4A*, *p14ARF*, *MTAP*, and *p15INK4B*; and mutation of *BAP1*.<sup>1</sup> The most useful potential genetic markers for diagnostic applications are for *p16* FISH and *BAP1* immunohistochemistry.

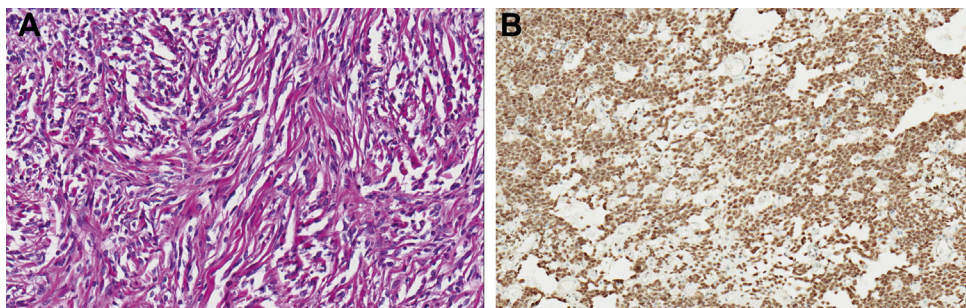
The loss of *p16INK4A* (also called *CDKN2A*) can be detected using FISH.<sup>29,30</sup> A number of studies have shown that *p16* loss by FISH is never seen in benign mesothelial processes, and this approach is therefore potentially a highly accurate method for separating benign from malignant mesothelial processes<sup>16,29–32</sup> (Fig. 5). The major limitation of *p16* detected by FISH is that the test only shows loss in a proportion of mesotheliomas, with better results (up to 100% of cases in some series<sup>32</sup>) for sarcomatoid mesotheliomas compared to epithelioid mesotheliomas; failure to find *p16* loss by FISH therefore does not make a process benign. The diagnostic finding of *p16* loss is homozygous deletion rather than heterozygous.<sup>16,29–32</sup>

It has been reported that there is a 100% concordance in *p16* FISH results between underlying invasive mesothelioma and surface mesothelial proliferations in the

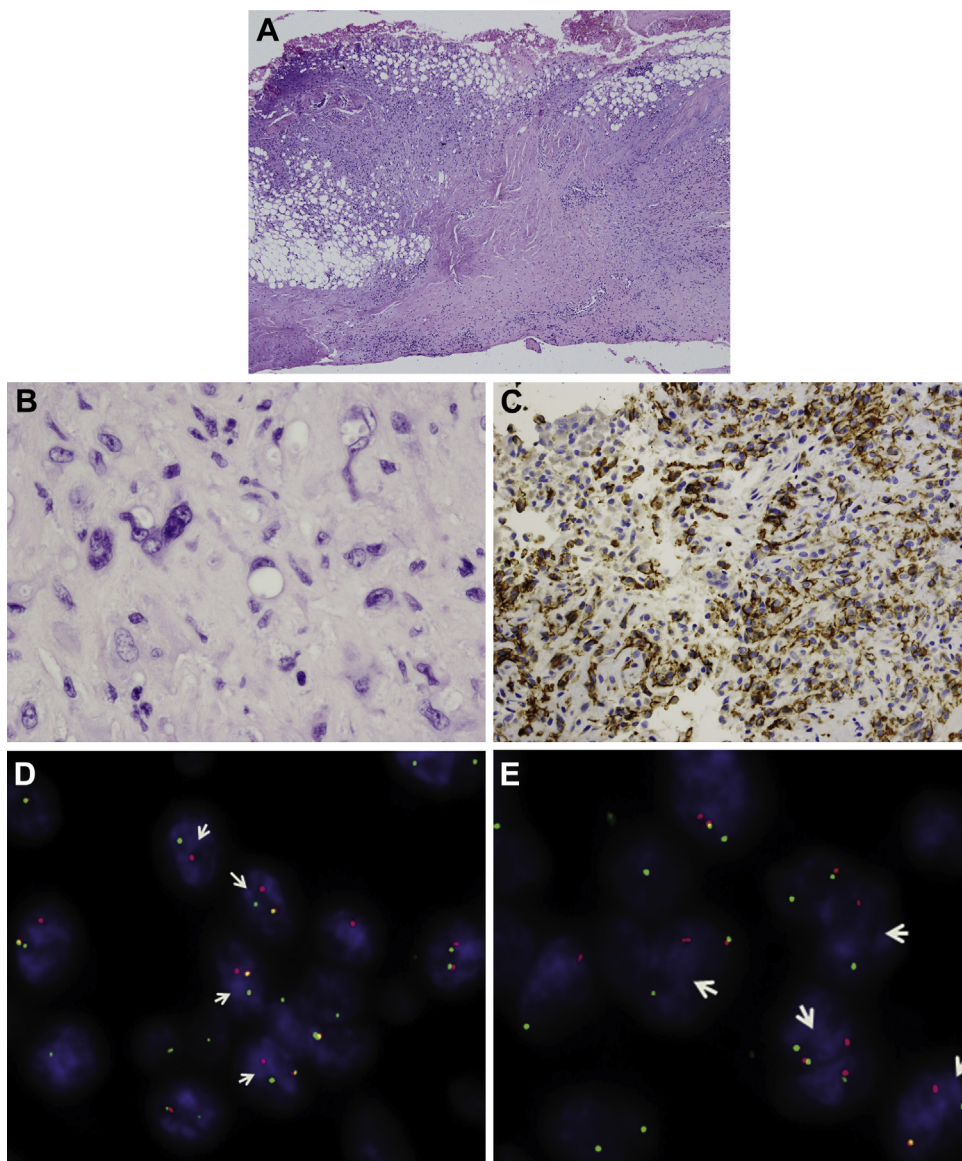
same case,<sup>17</sup> so that loss of *p16* by FISH is a potentially useful test when there is radiologic or direct visual evidence of pleural tumor, but biopsy specimens reveal only a surface proliferation. *p16* deletion by FISH has also been shown to be useful to favor DMM in cytologic specimens of pleural effusions in the setting of clinical and radiologic evidence of diffuse pleural thickening.<sup>33–35</sup> These results need confirmation from additional studies. This is important because differentiation of mesothelioma from benign mesothelial reactions may be difficult or even impossible in cytologic specimens.<sup>1</sup> The accuracy of purely cytologic diagnoses of malignant mesothelioma is fairly low compared to that of tissue diagnoses.<sup>9</sup>

Loss of *p16* by FISH is also correlated with a poorer prognosis.<sup>36,37</sup> It should be noted that *p16* immunohistochemistry does not give the same results and cannot be substituted for *p16* FISH,<sup>29</sup> although loss of *p16* immunohistochemical staining is also a marker of a poorer prognosis.<sup>36</sup>

The discovery of inactivating mutations in the *BAP1* gene in sporadic, and hereditary DMM has opened up a variety of novel molecular, clinical, and diagnostic investigations.<sup>38,39</sup> *BAP1* mutations are found in a substantial proportion of epithelioid mesotheliomas (roughly 40–60%), and a lesser proportion of sarcomatoid mesotheliomas (< 20%).<sup>40,41</sup>



**Figure 7.** Solitary fibrous tumor. (A) This neoplasm consists of spindle cells in a storiform pattern with a stroma showing prominent rosy collagen. (B) Immunohistochemistry for STAT6 shows diffuse strong nuclear staining.



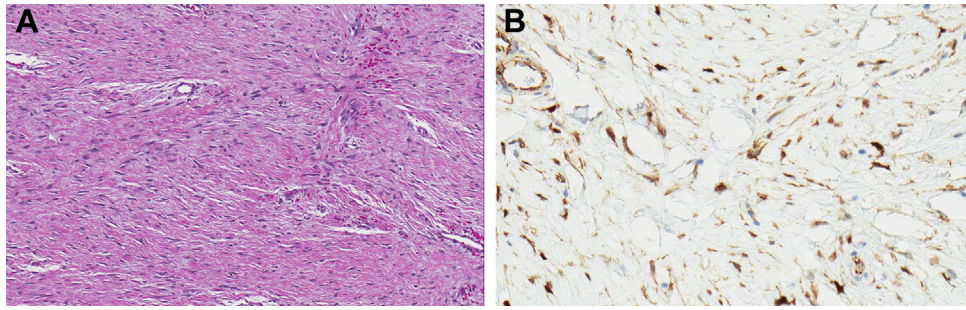
**Figure 8.** Epithelioid hemangioendothelioma. (A) The pleura is markedly thickened and infiltrated by a cellular neoplasm. There is extensive infiltration of parietal pleural fat. (B) The tumor has a hyaline stroma infiltrated by cytologically bland epithelioid cells with some intracytoplasmic lumens (center). (C) CD31 shows diffuse strong staining. (D and E) Fluorescence in situ hybridization analysis using custom BAC probes shows break-apart signals (arrows in CAMTA1 [D] and WWTR1 [E]). Red, centromeric; green, telomeric. (D and E, Courtesy of Dr. Cristina Antonescu.)

Most *BAP1* mutations are somatic, but a few (probably < 5%) represent germline mutations, and these patients or their kindred may also harbor ocular and cutaneous melanomas, renal cell carcinomas, and a variety of other tumors.<sup>38,39,42,43</sup> From a diagnostic perspective, this is a potentially useful marker because there is a reliable immunohistochemical marker and mutation of the gene results in loss of nuclear staining (Fig. 4).<sup>16,38,44,45</sup>

One promising diagnostic application includes the setting of separating DMMs from reactive mesothelial proliferations where they may play a role in conjunction with *p16* FISH.<sup>16,17,46</sup> Recent studies by Sheffield et al.,<sup>16</sup> Hwang et al.,<sup>17</sup> and Cigognetti et al.<sup>44</sup> suggest that loss of

*p16* detected by FISH and the loss of *BAP1* (Fig. 6A and B) detected by immunohistochemistry may be useful in separating malignant DMM from reactive pleuritis. Cigognetti et al.<sup>44</sup> found *BAP1* loss mostly in epithelioid DMMs rather than sarcomatoid tumors, suggesting that this feature is most useful in the differential diagnosis of epithelioid mesothelial proliferations. They also presented data suggesting that *BAP1* loss may be useful in cytologic specimens to favor the diagnosis of mesothelioma.<sup>44</sup> Sheffield et al.<sup>16</sup> combined *BAP1*/*p16* FISH results and found this to be a highly specific method of diagnosing malignant DMMs in the setting of problem cases in the distinction of benign versus malignant mesothelial





**Figure 9.** Desmoid tumor. (A) This tumor consists of bland spindle cells with sharply tapered nuclei growing within a fibrous stroma. (B) Immunohistochemistry for  $\beta$ -catenin shows positive nuclear staining.

proliferation, especially when invasion is difficult to demonstrate. This combination was also 58% sensitive for detecting malignancy.<sup>16</sup> Thus far, *BAP1* loss has not been seen in benign mesothelial reactions, and *BAP1* staining is a potentially useful approach to separating benign and malignant mesothelial processes<sup>16</sup>—but this issue needs further confirmation. As is true of *p16* FISH, not all mesotheliomas show *BAP1* loss, so failure to find loss of *BAP1* does not make a mesothelial process benign.<sup>16</sup> In addition, because the loss of *BAP1* by immunohistochemistry and deletion of *p16* detected by FISH are not only seen in mesothelioma but also in other tumors, it remains essential to apply standard criteria for the diagnosis of mesothelioma before using these tests.<sup>46</sup>

#### **STAT6 Immunohistochemical Marker for Solitary Fibrous Tumor**

Another useful discovery from a whole-exome sequencing study was that the *NAB2-STAT6* fusion is characteristic of solitary fibrous tumor.<sup>14,47</sup> SFTs are rare mesenchymal tumors that have distinctive histologic features (Fig. 7A), allowing for definitive diagnosis without the need for special stains. However, in some cases, the diagnosis is challenging, particularly in small biopsy specimens or when characteristic histologic patterns are not readily apparent. Using whole-exome sequencing, identification of the *NAB2-STAT6* fusion in SFT<sup>47,48</sup> led to the development of an antibody to STAT6, which shows nuclear reactivity (Fig. 7B) and is a useful diagnostic immunohistochemical marker.<sup>14</sup> However, it is not a specific marker, because it is also expressed in a small percentage of desmoid tumors and unclassified sarcomas that potentially could be confused with SFT.<sup>49</sup>

#### **WWTR1-CAMTA1 Fusion as a Marker for Epithelioid Hemangioendothelioma**

Another useful genetic discovery is the finding that most epithelioid hemangioendotheliomas have a specific translocation (i.e., [1;3](p36;q2325)), which results in *WWTR1-CAMTA1* gene fusion.<sup>50–52</sup> A small percentage of

these tumors may have a *YAP1-TFE3* fusion.<sup>53</sup> Epithelioid hemangioendothelioma is a low- to intermediate-grade malignant vascular tumor that can present in the pleura (Fig. 8A–C). Patients with tumors that present primarily as pleural masses have a significantly poorer prognosis than those that present as lung tumors.<sup>54</sup> Histologically, it is composed of cords, strands, or solid nests of epithelioid endothelial cells in a myxohyaline stroma.<sup>54,55</sup> They may be low- or intermediate-grade, with the latter distinguished by the presence of necrosis, increased mitotic activity (mean, 2/2 mm<sup>2</sup>), and greater nuclear atypia.<sup>54</sup> Epithelioid hemangioendotheliomas are distinguished from the high-grade and clinically more aggressive epithelioid angiosarcomas, which are more likely to show prominent capillary-like vasoformative elements, blood lakes, papillary growth, and prominent nucleoli.<sup>54</sup> In addition, epithelioid angiosarcomas typically lack *WWTR1-CAMTA1* fusions.<sup>54</sup> Immunohistochemistry for the vascular markers CD31 (Fig. 8C), CD34, ERG, and FLI1 can be useful in confirming the diagnosis. Focal cytokeratin expression is present in 25% to 30% of cases.<sup>54</sup> In some difficult cases, particularly in small biopsy specimens, FISH for the *WWTR1-CAMTA1* fusion (Fig. 8D and E) can be a valuable diagnostic tool.<sup>54</sup>

#### **CTNNB1 Mutation and $\beta$ -Catenin Immunohistochemistry in Desmoid-Type Fibromatosis**

Desmoid-type fibromatosis is a locally aggressive myofibroblastic neoplasm that can present in the pleura. These tumors are poorly defined, highly infiltrative masses that often invade soft tissues of the chest wall. Histologically, the tumors consist of cytologically uniform fibroblastic/myofibroblastic cells arranged in long fascicles within a fibrillary or hyalinized fibrous stroma (Fig. 9A). Tumor cells are ovoid or spindle-shaped. These tumors can express smooth muscle actin or muscle-specific actin. They can express nuclear  $\beta$ -catenin by immunohistochemistry in up to 75% of cases (Fig. 9B).<sup>25,56</sup> Sporadic desmoid-type fibromatosis have been shown to have catenin-associated protein  $\beta 1$  (*CTNNB1*) gene mutations in about 85% of



cases.<sup>26</sup> It has been suggested that *CTNNB1* mutations may be prognostic for local recurrence,<sup>57</sup> although this remains to be proven.<sup>26</sup>

## Summary

In summary, while the essential structure of the 2015 WHO Classification of Pleural Tumors is similar to that published in 2004, we review in this article some of the exciting genetic advances that have led to improved diagnostic methods.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at [www.jto.org](http://www.jto.org) and at <http://dx.doi.org/10.1016/j.jtho.2015.11.005>.

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